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Synthesis of Functionalized 1,4-Dioxanes with an Additional (Hetero)Aliphatic Ring

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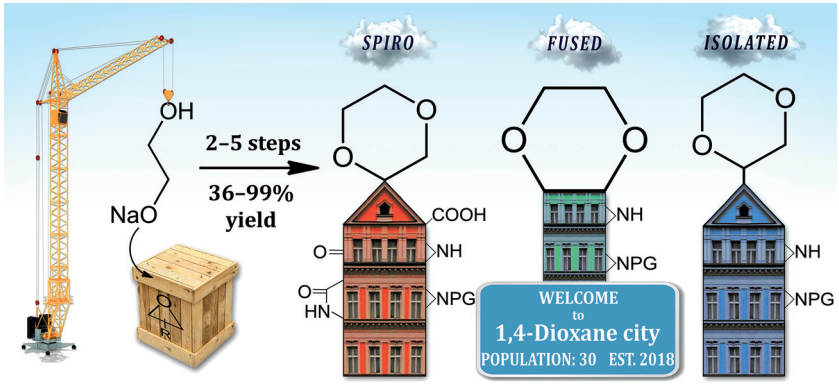

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Abstract An approach to the preparation of 2-mono-, 2,2- and 2,3-disubstituted 1,4-dioxane derivatives is described. The reaction sequence commences from readily available epoxides, in most cases prepared via the Corey–Chaikovsky reaction of the corresponding aldehydes and ketones. The key step of the method is epoxide ring opening with ethylene glycol monosodium salt, followed by further cyclization of the diols obtained. The utility of the approach was demonstrated by multigram preparation of novel functionalized 1,4-dioxanes bearing additional cycloalkane, piperidine or pyrrolidine rings, mostly spirocyclic compounds, which are advanced building blocks for medicinal chemistry.

Key words oxygen heterocycles, 1,4-dioxane, spiro compounds, building blocks, oxirane

Among recent tendencies in drug discovery, the shift from aromatic rings dominating in existing drugs towards compounds derived from saturated heterocycles has become popular because of the improving pharmacokinetics, solubility, or bioavailability of the target molecules.[1–7] In particular, 1,4-dioxane-containing scaffolds have proven their importance for organic synthesis and medicinal chemistry because of their occurrence in a number of natural products and pharmaceutical agents.[8–12] The 1,4-dioxane motif can be used as a bioisosteric replacement of carbocycles, as well as piperidine, piperazine or morpholine fragments in order to alter the number and strength of hydrogen-bond acceptors and overall hydrophilicity of the compound.

Examples of biologically active 1,4-dioxanes include spectinomycin (**1**; Figure 1),[13,14] a marketed antibiotic used for more than half a century, c-Met kinase inhibitor MK-2461 (**2**) with in vivo anticancer effect,[15] non-receptor tyrosine-protein kinase TYK2 inhibitor **3**,[16] inhibitors of epidermal growth factor-activated receptor (EGFR) **4**,[17] muscarinic receptor antagonists (e.g., **5**),[18–21] and antiviral agent **6**.[22]

Another feature of the 1,4-dioxane six-membered ring is its conformational restriction as compared to flexible open-chain counterparts or even structurally related 1,3-dioxolane analogues. Given this, *C*-substituted 1,4-dioxanes

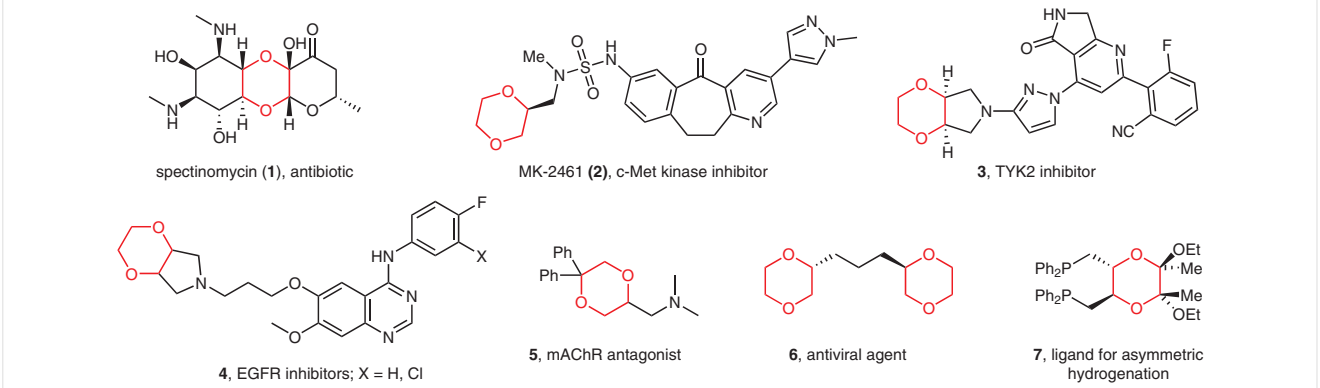
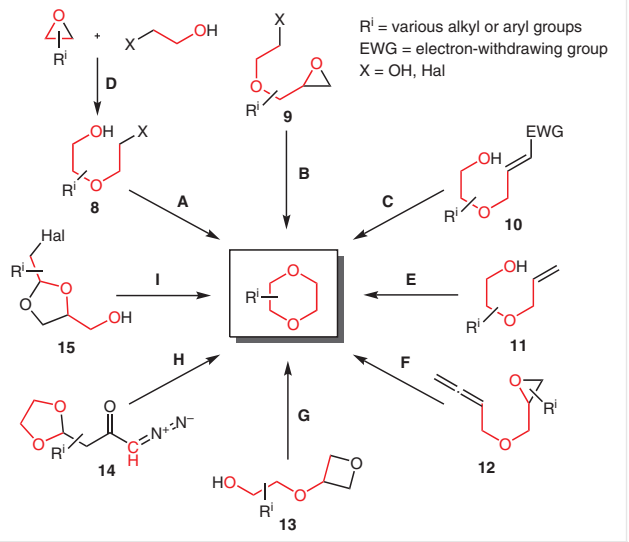


Figure 1 Some representatives of biologically active (**1**–**6**) and synthetically useful (**7**) 1,4-dioxane derivatives

can serve as useful chiral auxiliaries in asymmetric synthesis, for example, in the ligand **7**, which is widely used in asymmetric hydrogenation.[23]

Known methods for the synthesis of 1,4-dioxanes with aliphatic substituents can be divided into two large groups: those based on C–H bond modification[24–26] and on the construction of the heterocyclic ring. The most renowned approach falling into the latter category relies on intramolecular cyclizations of 1,2-diol derivatives **8**–**10** bearing an electrophilic moiety at the appropriate position (Scheme 1, pathways **A**,[18,27–32] **B**,[33–35] and **C**[19,36–39]). A variation of this strategy includes the oldest method in this series, namely dimerization of epichlorohydrin[40,41] and other epoxides,[42] as well as Lewis acid mediated reaction of epoxides with β-halohydrins[43–46] or 1,2-diols[47] (**D**), followed by intramolecular cyclization. Alternatively, intermediates of the type **8** could be generated by reaction of 1,2-diols and 1,2-dielectrophiles[48–51] or via dimerization of β-halohydrins.[52] Other methods included iodo-[35,53] or selenocyclization[54] of alkenes **11** (**E**), gold-promoted cyclization of allenyl epoxides **12** (**F**),[55] and recyclization of other oxygen-containing heterocycles **13**–**15** (**G**,[22] **H**[56–58] and **I**[20,21,59]).



Scheme 1 Known approaches to the construction of the substituted 1,4-dioxane ring

In this work, we have aimed at the preparation of functionalized 1,4-dioxanes with additional fused, spiro-connected or isolated (hetero)aliphatic rings (compounds **16**–**24** Figure 2), which are promising advanced building blocks for use in medicinal chemistry. Given that the corresponding oxiranes are more or less readily available, we have turned to the pathway **D+A** shown in Scheme 1 as a general strategy to achieve this goal.

The reported procedures for such transformations involved the use of Lewis acids as the reaction promoter for step **D**, which was not compatible with functionalized substrates of our interest. Therefore, we have considered basic reaction conditions; i.e., oxirane ring opening with ethylene glycol monosodium salt, followed by intramolecular diol cyclization.

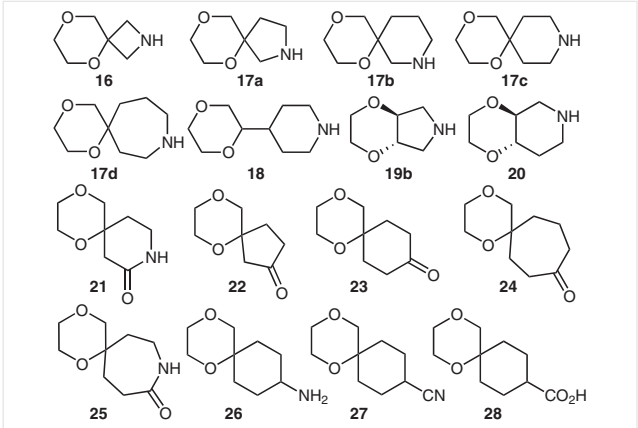
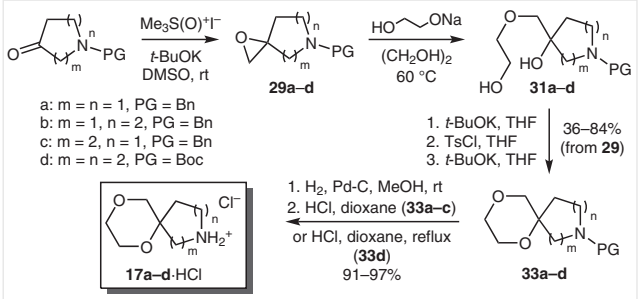
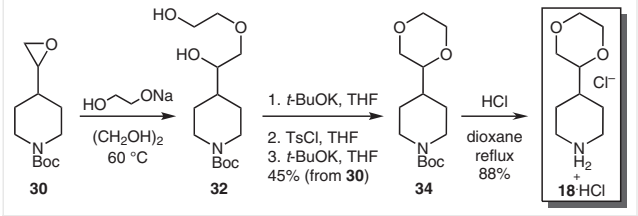


Figure 2 Target compounds of this work (relative configurations are shown)

To our knowledge, this approach was not described previously; hence, we have tested this idea for the preparation of spirocyclic 1,4-dioxanes **17a–d**, as well as compound **18** (Scheme 2 and Scheme 3).



Scheme 2 Synthesis of spirocyclic 1,4-dioxanes **17a–d**·HCl



Scheme 3 Synthesis of 4-(1,4-dioxan-2-yl)piperidine **18**·HCl

We started with synthesis of oxiranes **29a–d** and **30** using the reported method, namely a Corey–Chaikovsky reaction of the corresponding *N*-protected amino carbonyl compounds.[60–63] It was found that formation of the corresponding diols **31a–d** and **32** from oxiranes **29a–d** and **30**

proceeded smoothly at 60 °C in ethylene glycol as the solvent. The products **31a–d** and **32** were not obtained in pure form. Given their high hydrophilicity, they were not isolated by extractive methods; instead, solvent removal was performed by vacuum distillation. The crude **31a–d** and **32** were subjected to the next step, including tosylation and *t*-BuOK-mediated cyclization, which gave Boc or Bn derivatives **33a–d** and **34** in 36–85% overall yield. Notably, this reaction sequence could be easily performed in a one-pot manner, without isolation of the corresponding *O*-monotosylate intermediate. The use of tetrahydrofuran as the solvent was found to be optimal to achieve short reaction times (1–3 h), convenient work-up of the reaction mixture, and good yield of the product. Removal of the protective group in the molecules **33a–d** and **34** gave the target 1,4-dioxanes **17a–d**·HCl and **18**·HCl (88–97% yield).

It should be noted that aliphatic spirocyclic 1,4-dioxanes have not been reported to date (although the synthesis of related 2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine derivatives was described[64]).

Being inspired by these results, we introduced oxirane **35** into the reaction sequence described above for the synthesis of the known 1,4-dioxane **19** (Scheme 4).[43] Unfortunately, the key reaction sequence of the method gave modest yield of the corresponding *N*-Boc derivative **36** (ca. 6% by ^{1}H NMR). The target product **19** could be obtained at increased scale (starting from 116 g of **35**) after removal of the Boc protective group in **36** as ca. 9:1 mixture of diastereomers **19a**·HCl and **19b**·HCl. The major stereoisomer (**19a**·HCl) was isolated in 4.5% yield after recrystallization. The minor isomer (**19b**·HCl) could be obtained in trace amounts as a 1:1 mixture with **19a**·HCl from the mother liquor (0.5% total yield). Relative configuration assignment for **19a** and **19b** was based on analysis of $^3J_{H–H}$ coupling constants in their ^{1}H NMR spectra. It should be noted that other spectral data (including results of 2D NMR experiments) were not informative for the stereochemistry assignment because of the symmetry of both molecules **19a**·HCl (C_2 axis) and **19b**·HCl (plane of symmetry). In the case of **19a**, the values of $^3J_{H–H}$ coupling constants observed for the protons of the 5(7)-CH_2 groups and 4a(7a)-CH were 10.6 Hz and 6.8 Hz, which might be characteristic for the relatively rigid *trans*-hydrindane system (Figure 3).[65] For **19b**, the corresponding values were 5.3 Hz and 3.9 Hz, which might be expected for the more flexible *cis*-fused bicyclic ring system.

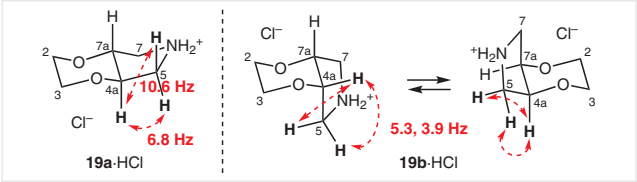
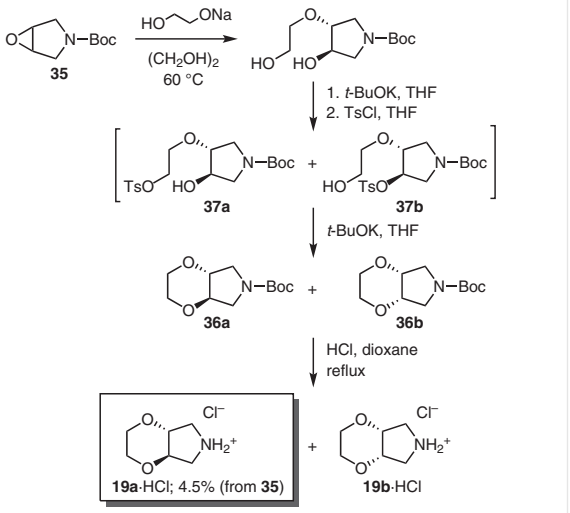


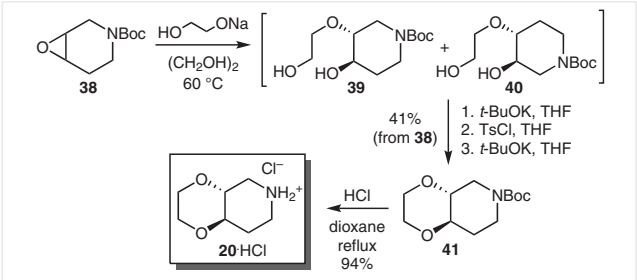
Figure 3 Informative $^3J_{H–H}$ coupling constants in ^{1}H NMR spectra of **19a**·HCl and **19b**·HCl

We believe that these results can be addressed to the relative strain observed in the transition state leading to the *trans*-fused bicyclic ring system of **36a**, which makes cyclization of the primary tosylate **37a** unfavorable. Instead, intermolecular reactions occur with **37a**, which presumably lead to the formation of unidentified oligo- and polymeric products. Formation of *cis*-isomer **19b**·HCl can be explained by participation of secondary tosylate **37b** (a minor product of the tosylation step), which undergoes cyclization with inversion of the configuration at the C-4 atom of the pyrrolidine ring.

Nevertheless, the developed method was effective with non-symmetric oxirane **38** (Scheme 5).[66] Reaction of **38** with ethylene glycol monosodium salt resulted in the formation of a mixture, presumably containing *trans*-diols **39** and **40**. It was not separated but subjected to the cyclization step, which gave the expected Boc derivative **41** (41% yield). The target 1,4-dioxane **20**·HCl was obtained after the subsequent deprotection step (94% yield). Relative *trans*-configuration of **20**·HCl was proven by NOESY experiment (Figure



Scheme 4 Synthesis of fused bicyclic 1,4-dioxanes **19**·HCl (relative configurations are shown)



Scheme 5 Synthesis of fused bicyclic 1,4-dioxane derivative **20**·HCl (relative configurations are shown)

4). In this case, *trans* fusion of two six-membered rings is favorable and does not result in the steric strain of the bicyclic system.

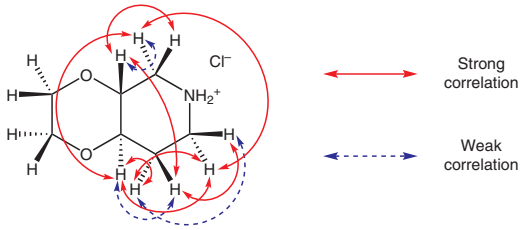
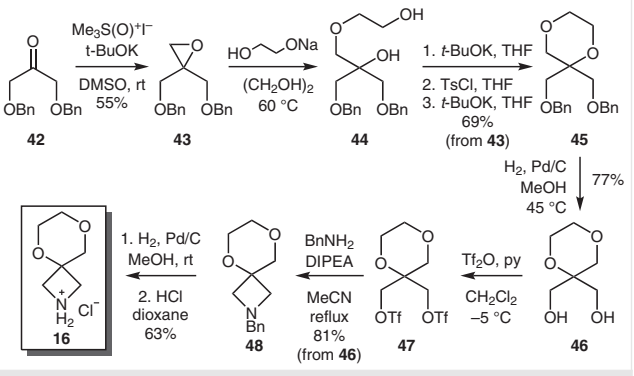


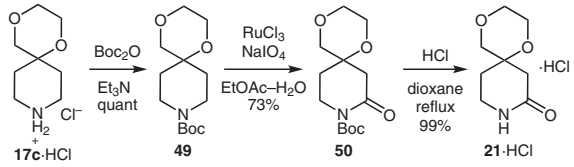
Figure 4 Representative correlations in NOESY spectrum of **20**·HCl

A slightly different approach was used for the preparation of azetidine-containing 1,4-dioxane **16**. The reaction sequence commenced from 1,3-bis(benzyloxy)propan-2-one (**42**)[67] as a convenient starting material with reasonable lipophilicity (Scheme 6). Compound **42** was converted into the corresponding oxirane **43** (55% yield) by using the Corey–Chaikovsky reaction. Further transformations followed the standard synthetic scheme described above; they included oxirane ring opening with ethylene glycol monosodium salt, tosylation and *t*-BuOK-mediated cyclization, and gave the 1,4-dioxane **45** in 69% overall yield. Subsequent debenzylation of **45** led to the corresponding 1,3-diol **46** (77% yield). The distilled diol **46** was subjected to the triflation step, which gave bis(trifluoromethanesulfonate) **47**in 98% yield. Construction of the azetidine ring was achieved through the double alkylation of benzylamine (81% yield), which gave **48**. The target spirocyclic 1,4-dioxane **16** was obtained after the catalytic hydrogenolysis of **48** (63% overall yield, as hydrochloride).



Scheme 6 Synthesis of 5,8-dioxa-2-azaspiro[3.5]nonane (**16**·HCl)

1,4-Dioxane-containing piperidone **21** was also prepared (Scheme 7). To achieve this, Boc derivative **49** (obtained from hydrochloride **17c**·HCl in quantitative yield) was oxidized with $RuCl_3$ to give imide **50** (73% yield). Subsequent deprotection of **50** gave the target compound **21** (99% yield, as hydrochloride). It should be noted that isolation of lactam **21** as the hydrochloride salt is unusual but not unprecedented.[68]



Scheme 7 Synthesis of spirocyclic 1,4-dioxane **21**

The remaining spirocyclic building blocks **22**–**28** were prepared through a common synthetic intermediate – ketone **23**. In turn, synthesis of **23** commenced from the known dispirocyclic oxirane **51**[69] and followed the methodology described above using ethylene glycol monosodium salt (Scheme 8). Compound **23** was obtained from **51** in three steps and 33% overall yield.

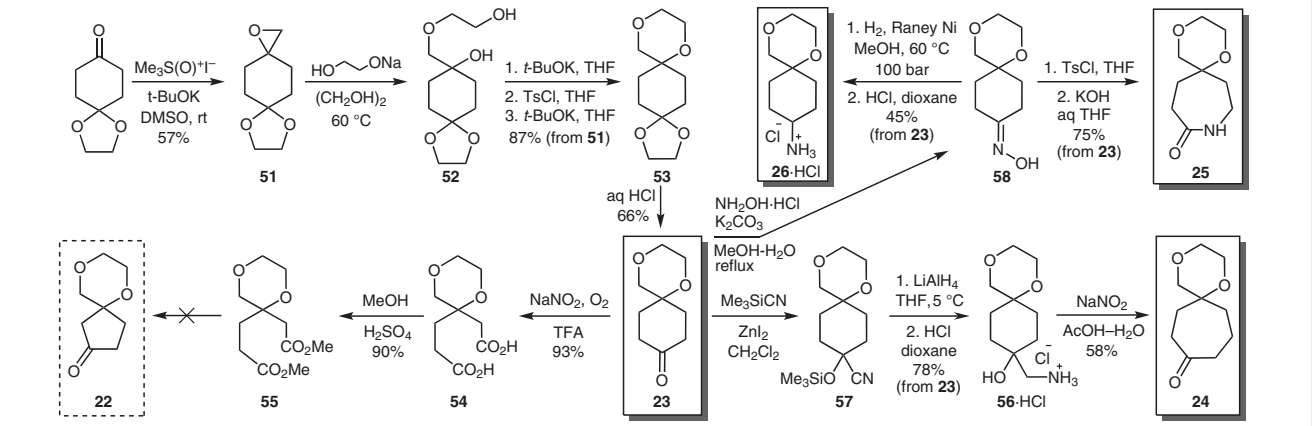
For the preparation of the homologues **22** and **24**, classical ring contraction/expansion reaction sequences were envisaged. To prepare **22**, the cyclohexanone ring in **23** was subjected to the oxidative cleavage with a $NaNO_2/O_2$/TFA system. Dicarboxylic acid **54** thus obtained (93% yield) was transformed into diester **55** (90% yield), which was introduced into the Dieckmann cyclization, followed by hydrolysis and decarboxylation. Unfortunately, the product **22** could not be obtained using this method.

For the synthesis of **24**, the Tiffeneau–Demjanov rearrangement of the corresponding amino alcohol **56** was used as the key step. Compound **56** was obtained by using a standard method involving TMS cyanohydrin **57** formation in quantitative yield and its subsequent reduction with $LiAlH_4$ (78% yield). Treatment of **56** with $NaNO_2$ in AcOH/H_2O gave the target spirocyclic cycloheptanone **24** in 58% yield.

An alternative approach to the ring expansion in the molecule of **23** was also tested; namely, Beckmann type rearrangement of the corresponding oxime **58** (in turn obtained from **23** in 92% yield, using the standard protocol). The method included tosylation of **58**, followed by base-catalyzed rearrangement, and led to the spirocyclic caprolactam analogue **25** (75% yield).

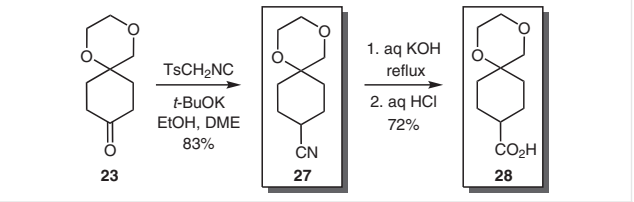
The oxime **58** was reduced to the corresponding primary amine **26** in methanolic solution over Raney nickel under 100 bar hydrogen (45% yield, isolated as hydrochloride). Compound **26** was obtained as ca. 2:1 mixture of diastereomers. Notably, using $LiAlH_4$ for this conversion was found to be ineffective because of the low yield of the product **26** (14%).

Finally, for the preparation of carboxylic acid **28**, ketone **23** was converted into the target nitrile **27** by treatment with tosylmethyl isocyanide (TosMIC) in 83% yield (Scheme 9). Alkaline hydrolysis of **27** gave the target compound **28** in 72% yield as ca. 1.2:1 mixture of diastereomers.



Scheme 8 Synthesis of spirocyclic 1,4-dioxanes **22–26**

In conclusion, recyclization of oxiranes upon reaction with ethylene glycol monosodium salt is an efficient protocol for the preparation of 2-mono-, 2,2- and 2,3-disubstituted 1,4-dioxanes. The scope of the method covers substrates bearing functional groups (i.e., protected amine or ketone), as well as 1,4-dioxanes with an additional fused, spiro-connected or isolated (hetero)aliphatic rings. It is shown that the products obtained can be subjected to some typical transformations, including ring contractions/expansions, which allows the scope of the approach to be extended to other functionalized 1,4-dioxanes (i.e., carboxylic acids and lactams). The target compounds are advanced building blocks for drug discovery; they can be prepared on a multigram scale and can therefore be considered as being readily available to organic and medicinal chemistry community.



Scheme 9 Synthesis of target compounds **27** and **28**

The solvents were purified according to the standard procedures. Oxiranes **29a–c**, **30**, **35**, **38** and **51** were prepared according to the reported methods. All other reagents and starting materials were obtained from commercial sources. Melting points were measured with a MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker 170 Avance 500 spectrometer (at 499.9 MHz for ^{1}H and 124.9 MHz for ^{13}C) and Varian Unity Plus 400 spectrometer (at 400.4 MHz for ^{1}H and 100.7 MHz for ^{13}C) in $CDCl_3$ or DMSO-d_6 solutions. Chemical shifts (δ) are given in ppm downfield from TMS as an internal standard. *J* values are reported in Hz. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, National Taras Shevchenko University of Kyiv. Mass spectra were recorded with an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI), electrospray ionization (CI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)). The purity of the prepared compounds was checked by GCMS with chemical ionization or by LCMS.

Ethylene Glycol Monosodium Salt

Ethylene glycol (300 g, 4.83 mol) and solid powdered NaOH (176 g, 4.39 mol) were mixed in xylenes (3 L) and stirred under reflux with a Dean–Stark trap until H_2O separation ceased (ca. 20 h). The mixture was cooled to r.t. and the precipitate was filtered, washed with xylenes (3 × 100 mL) and *t*-BuOMe (3 × 125 mL), dried in vacuo and stored under argon.

Yield: 390 g (96%); white powder.

Preparation of Epoxides 29d and 43; General Procedure

t-BuOK (80.0 g, 0.713 mol) was added in one portion to a stirred saturated solution of $Me_3SO^+I^-$ (196 g, 0.892 mol) in DMSO (600 mL) under argon atmosphere, and the mixture was stirred at r.t. until homogeneous (ca. 1 h). A solution of the corresponding ketone (0.594 mol) in THF (600 mL) was added dropwise to the stirred mixture at 15 °C for 1 h, then the mixture was stirred for 0.5 h, diluted with H_2O (1.5 L) and extracted with *t*-BuOMe (4 × 750 mL). The organic layer was washed with cold H_2O (4 × 250 mL), dried over Na_2SO_4 and evaporated in vacuo. The residue was dissolved in hexanes (750 mL) and washed with cold brine (4 × 150 mL). The organic phase was separated and evaporated in vacuo to give the corresponding oxiranes.

tert-Butyl 1-Oxa-6-azaspiro[2.6]nonane-6-carboxylate (29d)

Yield: 71.6 g (53%); yellowish liquid.

The compound existed as ca. 1:1 mixture of rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.67–3.47 (m, 2 H), 3.36–3.24 (m, 2 H), 2.69–2.52 (m, 2 H), 1.99–1.81 (m, 2 H), 1.79–1.62 (m, 4 H), 1.45 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.8, 78.9, 58.8 and 58.6, 54.6 and 54.3, 47.1 and 46.2, 42.8 and 42.6, 36.0 and 35.5, 33.3 and 33.1, 28.0, 23.6 and 23.3.

LC/MS (EI): *m*/*z* = 227 [M]$^+$.

Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.05; H, 9.13; N, 5.83.

2,2-Bis((benzyloxy)methyl)oxirane (43)

Yield: 92.9 g (55%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.22 (m, 10 H), 4.58 (d, *J* = 4.3 Hz, 4 H), 3.71 (d, *J* = 3.6 Hz, 4 H), 2.82 (d, *J* = 3.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.0, 128.4, 127.8, 127.7, 73.5, 70.1, 57.8, 48.8.

LC/MS (EI): *m*/*z* = 284 $[M]^+$.

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.75; H, 7.42.

Preparation of 33a–d, 34, 36, 41, 45, and 53; General Procedure

Ethylene glycol monosodium salt (40.0 g, 0.476 mol) was suspended in ethylene glycol (400 mL), and the corresponding oxirane (0.366 mol) was added in one portion under argon atmosphere. The mixture was heated at 60 °C overnight. H_2O (300 mL) and NH_4Cl (19.6 g, 0.366 mol) were added and the mixture was stirred for 1 h. Then most of H_2O was evaporated in vacuo, the residue was diluted with $CHCl_3$ (700 mL), stirred at r.t. for 1 h, and the precipitate was filtered off. The solvents were removed in vacuo, the residue was dissolved in $CHCl_3$ (500 mL), and the precipitate was filtered off once more. The solvent was evaporated in vacuo.

The residue was dissolved in THF (500 mL), and a THF solution (250 mL) of *t*-BuOK (39.4 g, 0.351 mol) was added in portions at r.t., and the mixture was stirred at r.t. for 1 h. Then a THF solution (400 mL) of TsCl (66.9 g, 0.351 mol) was added in one portion, and the mixture was stirred at r.t. for an additional 2 h. Then a THF solution (325 mL) of *t*-BuOK (49.3 g, 0.439 mol) was added and the resulting suspension was stirred for 1 h. H_2O (3.29 mL, 0.183 mol) was added, and most of THF was removed in vacuo. The residue was extracted with benzene (500 mL) and washed with cold brine (3 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated in vacuo.

2-Benzyl-6,9-dioxa-2-azaspiro[4.5]decane (33a)

Yield: 92.2 g (83%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 5 H), 3.70–3.59 (m, 6 H), 3.57 (s, 1 H), 3.52–3.42 (m, 1 H), 2.83 (d, *J* = 9.8 Hz, 1 H), 2.62 (t, *J* = 6.6 Hz, 2 H), 2.52 (d, *J* = 9.8 Hz, 1 H), 1.97–1.75 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.2, 128.2, 127.8, 126.5, 80.0, 72.9, 65.9, 62.1, 61.4, 59.8, 52.2, 33.9.

LC/MS (CI): *m*/*z* = 234 $[M + 1]^+$.

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.32; H, 8.01; N, 6.04.

8-Benzyl-1,4-dioxa-8-azaspiro[5.5]undecane (33b)

Yield: 74.2 g (63%); yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.22 (m, 5 H), 3.75–3.65 (m, 2 H), 3.65–3.58 (m, 4 H), 3.58–3.55 (m, 1 H), 3.51–3.45 (m, 1 H), 2.57–2.37 (m, 3 H), 2.37–2.29 (m, 1 H), 1.73 (d, *J* = 6.1 Hz, 2 H), 1.60–1.43 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.2, 128.9, 128.1, 127.0, 72.6, 70.3, 67.0, 63.1, 60.4, 57.9, 54.0, 30.9, 21.8.

LC/MS (CI): *m*/*z* = 248 $[M + 1]^+$.

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.63; H, 8.72; N, 5.92.

9-Benzyl-1,4-dioxa-9-azaspiro[5.5]undecane (33c)

Yield: 98.9 g (84%); yellowish solid; mp 52–54 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.22 (m, 5 H), 3.74–3.68 (m, 2 H), 3.68–3.62 (m, 2 H), 3.52 (d, *J* = 4.3 Hz, 2 H), 3.46 (d, *J* = 4.3 Hz, 2 H), 2.58–2.47 (m, 2 H), 2.38 (t, *J* = 10.2 Hz, 2 H), 1.91 (d, *J* = 13.4 Hz, 2 H), 1.64–1.51 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.4, 129.2, 128.2, 127.0, 74.7, 69.1, 67.1, 63.1, 59.8, 48.6, 31.2.

LC/MS (CI): *m*/*z* = 248 $[M + 1]^+$.

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.24; H, 8.88; N, 5.79.

***tert*-Butyl 1,4-Dioxa-9-azaspiro[5.6]dodecane-9-carboxylate (33d)**

Yield: 46.5 g (36%); yellowish oil.

The compound existed as ca. 1:1 mixture of rotamers.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.60–3.55 (m, 1 H), 3.54–3.45 (m, 4 H), 3.45–3.32 (m, 1 H), 3.26 (d, *J* = 11.4 Hz, 1 H), 3.23 (d, *J* = 11.4 Hz, 1 H), 3.20–3.09 (m, 1 H), 3.04 (t, *J* = 12.8 Hz, 1 H), 2.16 (dd, *J* = 14.7, 6.9 Hz, 1 H), 1.82–1.66 (m, 2 H), 1.62–1.52 (m, 1 H), 1.44–1.35 (m, 1 H), 1.34 (s, 9 H), 1.23–1.11 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.9, 78.5, 74.2, 71.8 and 71.7, 66.2, 59.7 and 59.5, 46.0 and 45.1, 39.8 and 39.5, 35.6 and 35.1, 29.7 and 29.3, 27.9, 19.9 and 19.2.

LC/MS (EI): *m*/*z* = 271 $[M]^+$.

Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 62.09; H, 9.10; N, 5.52.

***tert*-Butyl 4-(1,4-Dioxan-2-yl)piperidine-1-carboxylate (34)**

Yield: 58.1 g (45%); yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (s, 2 H), 4.09 (s, 2 H), 3.89–3.42 (m, 4 H), 3.37–3.24 (m, 1 H), 2.76–2.51 (m, 2 H), 1.97–1.74 (m, 1 H), 1.68–1.53 (m, 1 H), 1.54–1.47 (m, 1 H), 1.43 (s, 9 H), 1.30–1.12 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5, 79.1, 78.4, 69.3, 66.8, 66.5, 38.2, 28.3, 27.8, 27.4.

LC/MS (EI): *m*/*z* = 271 $[M]^+$.

Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 61.73; H, 9.46; N, 5.50.

***trans-tert*-Butyl Hexahydro[1,4]dioxino[2,3-*c*]pyridine-6(7*H*)-carboxylate (41)**

Yield: 47.5 g (41%); yellowish oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.15–3.80 (m, 2 H), 3.59 (s, 4 H), 3.11–3.02 (m, 1 H), 3.03–2.94 (m, 1 H), 2.64–2.28 (m, 2 H), 1.62 (d, *J* = 12.0 Hz, 1 H), 1.36–1.29 (m, 1 H), 1.27 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.8, 79.2, 78.2, 75.7, 66.6, 66.3, 45.6 and 44.9, 42.2 and 41.3, 28.9, 27.7.

LC/MS (EI): *m*/*z* = 243 $[M]^+$.

Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 58.99; H, 8.78; N, 6.01.

2,2-Bis((benzyloxy)methyl)-1,4-dioxane (45)

Yield: 107.9 g (69%); clear yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.20 (m, 10 H), 4.56 (s, 4 H), 3.81–3.69 (m, 4 H), 3.70–3.59 (m, 4 H), 3.57 (d, *J* = 9.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 128.4, 127.7, 127.6, 73.8, 73.6, 69.1, 68.5, 66.7, 60.9.

LC/MS (EI): *m*/*z* = 328 $[M]^+$.

Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.37; H, 7.28.

1,4,9,12-Tetraoxadispiro[4.2.5^8.2^5]pentadecane (53)

Yield: 88.7 g; yellowish oil. Used in the next step without purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.94–3.75 (m, 4 H), 3.66–3.49 (m, 4 H), 3.39–3.23 (m, 2 H), 1.99–1.67 (m, 4 H), 1.55–1.30 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 108.9, 74.6, 69.8, 67.0, 64.3, 62.1, 60.8, 29.5, 28.7.

Preparation of 16 and 17a–c; General Procedure

10% Pd/C (7.50 g) was added in portions to the corresponding *N*-benzyl derivative (0.300 mol) in 10% HCl in 1,4-dioxane (120 mL) at r.t. The mixture was stirred at r.t. for 30 min, the solvent was evaporated in vacuo to dryness. The resulting hydrochloride was dissolved in MeOH (750 mL) and the mixture was stirred vigorously under 1 atm of H_2 until the reaction was complete (monitored by ^{1}H NMR). The catalyst was filtered off, 10% HCl in 1,4-dioxane (150 mL) was added, and the mixture was evaporated in vacuo. The residue was triturated with *t*-BuOMe (500 mL) and filtered to give the target product as hydrochloride. If necessary, the product was recrystallized from *i*-PrOH or acetone/$CHCl_3$ (1:1).

5,8-Dioxa-2-azaspiro[3.5]nonane Hydrochloride (16·HCl)

Yield: 31.3 g (63%); grayish solid; mp 173–175 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.59 (br s, 2 H), 3.83 (s, 4 H), 3.76 (s, 2 H), 3.64–3.61 (m, 2 H), 3.56–3.53 (m, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 71.6, 69.9, 65.7, 62.8, 53.6.

LC/MS (CI): *m*/*z* = 130 $[M + 1]^+$.

Anal. Calcd for $C_6H_{12}ClNO_2$: C, 43.51; H, 7.30; N, 8.46; Cl, 21.40. Found: C, 43.72; H, 7.33; N, 8.35; Cl, 21.39.

6,9-Dioxa-2-azaspiro[4.5]decane Hydrochloride (17a·HCl)

Yield: 51.7 g (96%); yellowish crystals; mp 102–104 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.16–9.42 (m, 2 H), 3.73–3.49 (m, 6 H), 3.34–3.03 (m, 4 H), 2.13–1.99 (m, 1 H), 1.94–1.78 (m, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 80.1, 70.6, 66.3, 62.1, 50.5, 43.6, 32.5.

LC/MS (CI): *m*/*z* = 144 $[M + 1]^+$.

Anal. Calcd for $C_7H_{14}ClNO_2$: C, 46.80; H, 7.86; N, 7.80; Cl, 19.73. Found: C, 46.41; H, 7.88; N, 8.10; Cl, 19.66.

1,4-Dioxa-8-azaspiro[5.5]undecane Hydrochloride (17b·HCl)

Yield: 54.6 g (94%); white crystals; mp 160–162 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.89 (br s, 1 H), 8.47 (s, 1 H), 3.74 (m, 1 H), 3.67–3.46 (m, 4 H), 3.40 (d, *J* = 13.3 Hz, 1 H), 3.33 (d, *J* = 11.7 Hz, 1 H), 3.07 (d, *J* = 11.7 Hz, 1 H), 2.88 (t, *J* = 11.2 Hz, 1 H), 2.75 (m, 1 H), 1.87–1.67 (m, 2 H), 1.66–1.37 (m, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 71.9, 68.0, 66.6, 60.0, 45.1, 43.4, 28.3, 17.5.

LC/MS (CI): *m*/*z* = 158 $[M + 1]^+$.

Anal. Calcd for $C_8H_{16}ClNO_2$: C, 49.61; H, 8.33; N, 7.23; Cl, 18.30. Found: C, 49.31; H, 8.72; N, 7.30; Cl, 18.62.

1,4-Dioxa-9-azaspiro[5.5]undecane Hydrochloride (17c·HCl)

Yield: 56.4 g (97%); white crystals; mp 191–193 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.23 (s, 2 H), 3.62 (s, 2 H), 3.55 (s, 2 H), 3.39 (s, 2 H), 3.05 (d, *J* = 12.3 Hz, 2 H), 2.90 (t, *J* = 11.7 Hz, 2 H), 1.98 (d, *J*= 13.9 Hz, 2 H), 1.66 (t, *J* = 13.1 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 73.7, 67.4, 66.6, 59.9, 38.9, 27.6.

LC/MS (CI): *m*/*z* = 158 $[M + 1]^+$.

Anal. Calcd for $C_8H_{16}ClNO_2$: C, 49.61; H, 8.33; N, 7.23; Cl, 18.30. Found: C, 49.89; H, 7.99; N, 6.97; Cl, 18.37.

Preparation of 17d, 18, 19, and 20; General Procedure

10% HCl in 1,4-dioxane (95 mL) was added in one portion to the corresponding *N*-Boc derivative (0.170 mol), and the mixture was heated at reflux upon stirring for 15 min. Then the solvent was removed in vacuo, and the residue was recrystallized from acetone or acetone/$CHCl_3$ (1:1).

1,4-Dioxa-9-azaspiro[5.6]dodecane Hydrochloride (17d·HCl)

Yield: 32.1 g (91%); white crystals; mp 156–158 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.34 (s, 1 H), 9.26 (s, 1 H), 3.62–3.40 (m, 4 H), 3.33 (d, *J* = 11.4 Hz, 1 H), 3.27 (d, *J* = 11.4 Hz, 1 H), 3.17–2.89 (m, 4 H), 2.16–1.99 (m, 1 H), 1.96–1.62 (m, 4 H), 1.62–1.47 (m, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 73.6, 72.3, 66.5, 59.9, 45.6, 39.1, 33.2, 29.5, 18.9.

LC/MS (CI): *m*/*z* = 172 $[M + 1]^+$.

Anal. Calcd for $C_9H_{18}ClNO_2$: C, 52.05; H, 8.74; N, 6.74; Cl, 17.07. Found: C, 51.94; H, 8.80; N, 6.71; Cl, 17.07.

4-(1,4-Dioxan-2-yl)piperidine Hydrochloride (18·HCl)

Yield: 31.1 g (88%); white crystals; mp 177–179 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.29 (s, 1 H), 9.01 (s, 1 H), 3.71 (d, *J* = 8.9 Hz, 2 H), 3.61 (d, *J* = 11.2 Hz, 1 H), 3.53 (t, *J* = 11.2 Hz, 1 H), 3.40 (t, *J* = 11.2 Hz, 1 H), 3.29–3.11 (m, 4 H), 2.76 (d, *J* = 11.2 Hz, 2 H), 1.85 (d, *J* = 13.2 Hz, 1 H), 1.62 (d, *J* = 11.2 Hz, 2 H), 1.55–1.38 (m, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 77.8, 68.9, 66.7, 66.3, 43.2, 43.0, 35.5, 24.5, 24.4.

LC/MS (CI): *m*/*z* = 172 $[M + 1]^+$.

Anal. Calcd for $C_9H_{18}ClNO_2$: C, 52.05; H, 8.74; N, 6.74; Cl, 17.07. Found: C, 52.18; H, 9.04; N, 6.98; Cl, 17.47.

***trans*-Hexahydro-2*H*-[1,4]dioxino[2,3-*c*]pyrrole Hydrochloride (19a·HCl)**

Obtained by recrystallization of the crude product from acetone/$CHCl_3$.

Yield: 4.35 g (4.5% from oxirane **35**); yellowish crystals; mp 235–237 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.78 (s, 2 H, NH_2^+), 3.85 (dd, *J* = 11.2, 8.4 Hz, 2 H, 2- and 3-C*H*H), 3.67 (dd, *J* = 11.2, 8.4 Hz, 2 H, 2- and 3-CH*H*), 3.61–3.51 (m, 2 H, 4a- and 7a-C*H*), 3.39 (dd, *J* = 10.6, 6.8 Hz, 2 H, 5- and 7-C*H*H), 2.88 (t, *J* = 10.6 Hz, 2 H, 5- and 7-CH*H*).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 76.5 (2- and 3-CH_2), 66.9 (4a- and 7a-CH_2), 42.6 (5- and 7-CH_2).

LC/MS (CI): *m*/*z* = 130 $[M + 1]^+$.

Anal. Calcd for $C_6H_{12}ClNO_2$: C, 43.51; H, 7.30; N, 8.46; Cl, 21.40. Found: C, 43.28; H, 7.21; N, 8.49; Cl, 21.46.

cis- and *trans*-Hexahydro-2*H*-[1,4]dioxino[2,3-*c*]pyrrole Hydrochlorides (19b·HCl and 19a·HCl)

A 1:1 mixture of **19a**·HCl and **19b**·HCl was obtained from the mother liquor after recrystallization of the crude product **19**·HCl.

Yield: 483 mg (0.5% from oxirane **35**); white crystals; mp 183–185 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ (only for **19b**·HCl) = 9.83 (s, 2 H), 4.30–4.16 (m, 2 H), 3.78–3.71 (m, 2 H), 3.39–3.35 (m, 2 H), 3.28 (dd, *J* = 11.9, 3.9 Hz, 2 H), 3.21 (dd *J* = 11.9, 5.3 Hz, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ (only for **19b**·HCl) = 71.9, 61.9, 44.5.

LC/MS (CI): *m*/*z* = 130 [M + 1]$^+$.

Anal. Calcd for $C_6H_{12}ClNO_2$: C, 43.51; H, 7.30; N, 8.46; Cl, 21.40. Found: C, 43.24; H, 6.97; N, 8.77; Cl, 21.37.

trans-Octahydro-[1,4]dioxino[2,3-*c*]pyridine Hydrochloride (20·HCl)

Yield: 28.7 g (94%); white crystals; mp 174–176 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.82–9.45 (m, 2 H), 3.75 (t, *J* = 7.3 Hz, 2 H), 3.69–3.57 (m, 2 H), 3.56–3.46 (m, 1 H), 3.42–3.30 (m, 1 H), 3.21 (t, *J* = 11.5 Hz, 2 H), 3.01–2.87 (m, 1 H), 2.81–2.66 (m, 1 H), 1.88 (d, *J* = 12.3 Hz, 1 H), 1.70 (qd, *J* = 13.2, 4.1 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 75.9, 73.7, 67.0, 66.9, 44.4, 42.3, 26.6.

LC/MS (CI): *m*/*z* = 144 [M + 1]$^+$.

Anal. Calcd for $C_7H_{14}ClNO_2$: C, 46.80; H, 7.86; N, 7.80. Found: C, 46.61; H, 7.96; N, 7.63.

(1,4-Dioxane-2,2-diyl)dimethanol (46)

10% Pd-C (2.58 g) was added to a solution of **45** (12.9 g, 39.3 mmol) in MeOH (150 mL). The mixture was vigorously stirred under 1 atm of H_2 at 45 °C until the reaction was complete. The catalyst was filtered off and the mixture was evaporated in vacuo.The crude product was distilled in vacuo.

Yield: 4.48 g (77%); clear colorless oil; bp 138–141 °C/1 mmHg.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.72–3.62 (m, 6 H), 3.59–3.53 (m, 4 H), 3.53–3.47 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 73.9, 67.9, 66.5, 61.6, 60.8.

LC/MS (EI): *m*/*z* = 148 [M]$^+$.

Anal. Calcd for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: C, 48.78; H, 8.39.

(1,4-Dioxane-2,2-diyl)bis(methylene) Bis(trifluoromethanesulfonate) (47)

A solution of Tf_2O (8.75 mL, 52.0 mmol) in CH_2Cl_2 (50 mL) was added dropwise to a stirred solution of 1,3-diol **46** (3.50 g, 23.6 mmol) and pyridine (4.75 mL, 59.1 mmol) in CH_2Cl_2 (30 mL) at –5 °C. The mixture was stirred for 2 h, then the solution was washed with brine (3 × 25 mL). The organic phase was separated, dried over anhydrous Na_2SO_4 and evaporated in vacuo at r.t. The crude product was used in the next step without thorough characterization.

Yield: 9.54 g; pinkish amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.70 (d, *J* = 10.5 Hz, 2 H), 4.48 (d, *J* = 10.5 Hz, 2 H), 3.83 (s, 2 H), 3.73 (s, 2 H), 3.67 (s, 2 H).

2-Benzyl-5,8-dioxa-2-azaspiro[3.5]nonane (48)

A solution of bis(trifluoromethanesulfonate) **47** (9.04 g, 21.9 mmol), benzylamine (2.82 g, 26.3 mmol) and DIPEA (9.55 mL, 54.8 mmol) in acetonitrile (225 mL) was heated at reflux upon stirring for 2 d. The mixture was evaporated in vacuo, the residue was dissolved in *t*-BuOMe (450 mL) and washed with brine (3 × 100 mL). The organic phase was separated, dried over anhydrous Na_2SO_4 and evaporated in vacuo.

Yield: 3.88 g (81%); clear yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.18 (m, 5 H), 3.79 (s, 2 H), 3.70 (s, 2 H), 3.63 (s, 4 H), 3.46 (d, *J* = 8.7 Hz, 2 H), 2.98 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.7, 128.4, 128.4, 127.2, 71.9, 70.7, 66.2, 63.5, 62.9, 62.0.

LC/MS (CI): *m*/*z* = 220 [M + 1]$^+$.

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.41; H, 7.79; N, 6.56.

tert-Butyl 1,4-Dioxa-9-azaspiro[5.5]undecane-9-carboxylate (49)

Boc_2O (27.4 mL, 0.119 mol) was added dropwise to a stirred solution of amine hydrochloride **17c** (22.4 g, 0.116 mol) and Et_3N (31.8 mL, 0.228 mol) in MeOH (300 mL) at r.t. The mixture was stirred for an additional 30 min, and the solvent was evaporated in vacuo. The residue was dissolved in benzene (400 mL) and washed with H_2O (3 × 75 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated in vacuo.

Yield: 29.8 g (quant); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.61–3.54 (m, 2 H), 3.54–3.51 (m, 2 H), 3.49–3.46 (m, 2 H), 3.25 (s, 2 H), 2.97 (t, *J* = 11.4 Hz, 2 H), 1.72 (d, *J* = 13.6 Hz, 2 H), 1.28 (s, 9 H), 1.26–1.19 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.1, 78.6, 73.9, 68.5, 66.3, 59.3, 30.4, 27.8.

LC/MS (EI): *m*/*z* = 257 [M]$^+$.

Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.63; H, 9.39; N, 5.73.

tert-Butyl 8-Oxo-1,4-dioxa-9-azaspiro[5.5]undecane-9-carboxylate (50)

$RuCl_3$ (0.24 g, 1.16 mmol) in H_2O (5 mL) was added in one portion to a mixture of **49** (29.4 g, 0.114 mol) and $NaIO_4$ (53.8 g, 0.251 mol) in H_2O (500 mL) and EtOAc (1.5 L) at r.t. The resulting mixture was stirred for 2 d, then additional EtOAc (900 mL) was added to the solution, the organic phase was separated, dried over Na_2SO_4 and evaporated in vacuo. The residue was recrystallized from pentane.

Yield: 22.6 g (73%); white solid; mp 112–114 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.63–3.59 (m, 4 H), 3.57 (d, *J* = 4.8 Hz, 2 H), 3.38 (d, *J* = 4.4 Hz, 2 H), 2.69–2.61 (m, 1 H), 2.37 (d, *J* = 16.6 Hz, 1 H), 1.64 (dt, *J* = 15.2, 8.0 Hz, 1 H), 1.42 (s, 9 H), 1.37–1.34 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.2, 151.6, 82.4, 72.5, 69.9, 66.0, 60.0, 41.7, 41.1, 28.2, 27.4.

LC/MS (EI): *m*/*z* = 271 [M]$^+$.

Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.71; H, 7.95; N, 5.34.

1,4-Dioxa-9-azaspiro[5.5]undecan-8-one Hydrochloride (21·HCl)

10% HCl in 1,4-dioxane (45 mL) was added in one portion to *N*-Boc-amide **50** (22.1 g, 81.5 mmol), and the mixture was heated at reflux for 1 h. Then the solvent was removed in vacuo to give **21** as the hydrochloride.

Yield: 13.8 g (99%); white crystals; mp 152–154 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.73 (br s, 1 H), 7.86 (s, 1 H), 3.69–3.48 (m, 4 H), 3.44 (d, *J* = 11.4 Hz, 1 H), 3.33 (d, *J* = 11.4 Hz, 1 H), 3.24–3.12 (m, 1 H), 3.12–3.03 (m, 1 H), 2.31–2.18 (m, 2 H), 2.19–2.09 (m, 1 H), 1.66–1.51 (m, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.7, 72.8, 70.2, 66.4, 60.3, 38.9, 37.1, 26.2.

GC/MS (EI): *m*/*z* = 171 [M]$^+$.

Anal. Calcd for $C_8H_{14}ClNO_3$: C, 46.27; H, 6.80; N, 6.75; Cl, 17.07. Found: C, 46.45; H, 6.72; N, 6.80; Cl, 17.26.

1,4-Dioxaspiro[5.5]undecan-9-one (23)

37% aq HCl (0.45 mL) was added to a solution of ketal **53** (86.5 g, 0.404 mol) in acetone (500 mL). The mixture was heated at reflux for 1 h, then cooled to r.t. and evaporated in vacuo. The residue was distilled in vacuo to give pure ketone.

Yield: 45.4 g (66%); clear yellowish oil; bp 87–89 °C/1 mmHg.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.72–3.63 (m, 2 H), 3.63–3.54 (m, 2 H), 3.43 (s, 2 H), 2.48–2.35 (m, 2 H), 2.21–2.01 (m, 4 H), 1.66 (td, *J* = 13.7, 4.8 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 210.9, 73.5, 69.6, 66.7, 60.3, 36.0, 30.2.

GC/MS (EI): *m*/*z* = 170 [M]$^+$.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.11; H, 8.58.

3-(2-(Carboxymethyl)-1,4-dioxan-2-yl)propanoic Acid (54)

Ketone **23** (9.91 g, 58.2 mmol) was dissolved in TFA (100 mL), and $NaNO_2$ (16.1 g, 0.233 mol) was added in small portions to the stirred solution under air continuous flow. The mixture was stirred at 25 °C for 4 h and evaporated in vacuo. The residue was diluted with EtOAc (250 mL), insoluble inorganic compounds were filtered off, and the solvent was evaporated in vacuo.

Yield: 11.3 g (93%); yellowish solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.17 (s, 2 H), 3.66 (d, *J* = 8.4 Hz, 1 H), 3.58–3.48 (m, 3 H), 3.42 (d, *J* = 11.5 Hz, 1 H), 3.33 (s, 1 H), 2.60–2.51 (m, 1 H), 2.48–2.41 (m, 1 H), 2.30–2.18 (m, 2 H), 2.08–1.85 (m, 1 H), 1.81–1.68 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.9, 172.1, 72.3, 72.1, 66.4, 60.3, 38.3, 28.6, 27.8.

LC/MS (CI): *m*/*z* = 217 [M – 1]$^-$.

Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 49.48; H, 6.29.

Methyl 3-(2-(2-Methoxy-2-oxoethyl)-1,4-dioxan-2-yl)propanoate (55)

96% H_2SO_4 (0.5 mL, 4.63 mmol) was added to a solution of dicarboxylic acid **54** (10.1 g, 46.3 mmol) in anhydrous MeOH (100 mL). The solution was stirred for 2 h and evaporated in vacuo. The residue was diluted with $CHCl_3$ (350 mL) and washed with saturated aq $NaHCO_3$ (3 × 50 mL). The organic phase was separated, dried over Na_2SO_4 and evaporated in vacuo.

Yield: 10.3 g (90%); brownish liquid; bp 126–127 °C/1 mmHg.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.78–3.72 (m, 1 H), 3.69–3.61 (m, 10 H), 3.51 (dd, *J* = 11.5, 1.8 Hz, 1 H), 2.72 (dd, *J* = 14.3, 1.9 Hz, 1 H), 2.62 (dd, *J* = 14.3, 1.9 Hz, 1 H), 2.45–2.36 (m, 2 H), 2.24–2.13 (m, 1 H), 1.94–1.83 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.8, 170.6, 72.3, 72.2, 66.6, 60.6, 51.7, 51.7, 38.1, 28.4, 27.6.

LC/MS (CI): *m*/*z* = 246 [M]$^+$.

Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.61; H, 7.56.

9-((Trimethylsilyl)oxy)-1,4-dioxaspiro[5.5]undecane-9-carbonitrile (57)

TMSCN (7.30 mL, 58.4 mmol) was added dropwise to a stirred solution of cyclohexanone **23** (6.62 g, 38.9 mmol) and ZnI_2 (3.74 g, 11.7 mmol) in CH_2Cl_2 (75 mL) at 5 °C. The mixture was stirred overnight at r.t. and evaporated in vacuo. The residue was diluted with *t*-BuOMe (250 mL) and filtered. The filtrate was evaporated in vacuo and the crude product was used in the next step without further characterization.

Yield: 10.5 g; yellowish liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.67 (s, 2 H), 3.62 (s, 2 H), 3.47 (s, 2 H), 2.07 (d, *J* = 13.0 Hz, 2 H), 1.99–1.78 (m, 4 H), 1.41 (t, *J* = 10.1 Hz, 2 H), 0.19 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 121.7, 74.6, 71.9, 68.6, 67.3, 59.8, 33.6, 28.1, 1.5.

9-(Aminomethyl)-1,4-dioxaspiro[5.5]undecan-9-ol Hydrochloride (56·HCl)

Cyanohydrin derivative **57** (7.50 g) from the previous step was added in small portions to a vigorously stirred suspension of $LiAlH_4$ (2.11 g, 55.7 mmol) in THF (150 mL) at 5 °C. The mixture was stirred overnight at r.t., then 10% aq KOH (12.5 g, 0.223 mmol) was added dropwise. The resulting mixture was filtered, 10% HCl in 1,4-dioxane (200 mL) was added to the combined filtrates, and the solution was evaporated in vacuo. The residue was recrystallized from acetone.

Yield 5.16 g (78% from **23**); white powder; mp 172–174 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.01 (br s, 3 H), 4.99 (s, 1 H), 3.61–3.55 (m, 2 H), 3.53–3.48 (m, 2 H), 3.41–3.37 (m, 2 H), 2.77 (d, *J* = 4.4 Hz, 2 H), 1.72–1.62 (m, 2 H), 1.60–1.52 (m, 2 H), 1.51–1.44 (m, 2 H), 1.44–1.40 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 72.8, 70.4, 68.7, 66.7, 61.2, 59.7, 46.4, 30.5, 29.7, 27.7.

LC/MS (CI): *m*/*z* = 202 [M + 1]$^+$.

Anal. Calcd for $C_{10}H_{20}ClNO_3$: C, 50.53; H, 8.48; N, 5.89; Cl, 14.91. Found: C, 50.19; H, 8.80; N, 5.94; Cl, 14.90.

1,4-Dioxaspiro[5.6]dodecan-9-one (24)

Amino alcohol **56**·HCl (4.25 g, 17.9 mmol) was dissolved in 50% aq AcOH (210 mL), and $NaNO_2$ (1.27 g, 18.4 mmol) in H_2O (19.0 mL) was added dropwise at 0 °C with stirring. The reaction mixture was warmed to r.t. upon stirring overnight, then diluted with $CHCl_3$ (500 mL), washed with H_2O (3 × 75 mL) and saturated aq $NaHCO_3$ (3 × 50 mL). The organic phase was separated, dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo to give crude **24**, which was purified by distillation in vacuo. Microanalytical sample was obtained by reverse-phase HPLC (Poroshell 120 SBC_{18}, 4.6 × 30 mm column, gradient MeCN/H_2O as eluent).

Yield: 1.91 g (58%); clear yellowish oil; bp 135–137 °C/1 mmHg.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.62 (m, 4 H), 3.38 (d, *J* = 2.5 Hz, 2 H), 2.77 (t, *J* = 12.7 Hz, 1 H), 2.55–2.46 (m, 1 H), 2.41 (m, 1 H), 2.30 (d, *J* = 6.8 Hz, 1 H), 2.25 (d, *J* = 6.2 Hz, 1 H), 2.19–2.11 (m, 1 H), 1.94–1.87 (m, 1 H), 1.68–1.62 (m, 1 H), 1.55–1.50 (m, 1 H), 1.24 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 214.2, 75.0, 71.9, 66.8, 60.2, 43.5, 36.2, 35.8, 28.2, 17.1.

LC/MS (CI): *m*/*z* = 184 [M]$^+$.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.18; H, 8.87.

1,4-Dioxaspiro[5.5]undecan-9-one Oxime (58)

A mixture of **23** (80.0 g, 0.470 mol), hydroxylamine hydrochloride (49.0 g, 0.705 mol), and K_2CO_3 (77.9 g, 0.564 mol) in MeOH/H_2O (1:1 v/v, 600 mL) was heated at reflux overnight. Most of the MeOH was evaporated in vacuo, additional H_2O (300 mL) was added to residue, which was extracted with $CHCl_3$ (900 mL). The organic phase was separated, dried over Na_2SO_4, and the solvent was evaporated in vacuo. The crude product was recrystallized from hexanes and used without further purification.

Yield: 79.2 g; yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (s, 1 H), 3.76–3.68 (m, 2 H), 3.68–3.64 (m, 2 H), 3.16 (d, *J* = 18.8 Hz, 1 H), 3.07–2.95 (m, 1 H), 2.44–2.34 (m, 1 H), 2.20–2.09 (m, 3 H), 1.95–1.49 (m, 2 H), 1.42–1.31 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.8, 99.5, 74.1, 69.7, 66.5, 59.5, 47.1, 27.2, 26.5.

LC/MS (CI): *m*/*z* = 186 $[M + 1]^+$.

1,4-Dioxa-9-azaspiro[5.6]dodecan-10-one (25)

TsCl (27.2 g, 0.142 mol) was added to a vigorously stirred solution of oxime **58** (26.9 g) from the previous step and KOH (29.4 g, 0.523 mol) in THF/H_2O (3:1, 1.2 L) at 0 °C. The mixture was warmed to r.t. upon stirring overnight. Then, most of THF was evaporated in vacuo, and the residue was extracted with $CHCl_3$ (600 mL). The organic phase was separated, dried over anhydrous Na_2SO_4 and the solvent was evaporated in vacuo. The obtained crude product was recrystallized from hexanes.

Yield: 20.2 g (75% from **23**); white crystals; mp 107–109 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.42 (s, 1 H), 3.71–3.45 (m, 4 H), 3.44–3.18 (m, 2 H), 2.90–2.74 (m, 1 H), 2.60 (t, *J* = 13.0 Hz, 1 H), 2.12–2.00 (m, 1 H), 2.00–1.81 (m, 2 H), 1.37 (t, *J* = 13.4 Hz, 1 H), 1.29 (t, *J* = 13.4 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 177.1, 74.7, 71.3, 66.7, 59.5, 35.3, 35.1, 29.2, 27.8.

GC/MS (EI): *m*/*z* = 185 $[M]^+$.

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.37; H, 7.81; N, 7.31.

1,4-Dioxaspiro[5.5]undecan-9-amine Hydrochloride (26·HCl)

Oxime **58** (35.0 g) from the previous step was dissolved in MeOH (1.2 L), and Raney nickel (15 g) was added to the resulting solution in an autoclave. The mixture was heated at 100 bar of H_2 and 60 °C for 8 h. Then the reaction mixture was cooled, the catalyst was filtered off, and the combined filtrates were evaporated in vacuo. 10% HCl in 1,4-dioxane (30 mL) was added to the residue, and the mixture was evaporated to dryness. The residue was recrystallized from acetone.

Yield: 17.7 g (45% from **23**); white powder; mp 190–192 °C.

The compound was obtained as ca. 2:1 mixture of diastereomers.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.15 (br s, 0.33 × 3 H) and 8.09 (br s, 0.67 × 3 H), 3.69–3.46 (m, 4 H), 3.43 (s, 0.33 × 2 H) and 3.29 (s, 0.67 × 2 H), 3.20–3.09 (m, 0.33 × 1 H) and 3.02–2.86 (m, 0.67 × 1 H), 2.06–1.62 (m, 4 H), 1.59–1.09 (m, 4 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 74.6, 72.1, 70.1, 69.0, 66.8 and 66.7, 59.9 and 59.6, 49.5, 48.1, 28.8 and 28.0, 25.2 and 25.0.

LC/MS (CI): *m*/*z* = 172 $[M + 1]^+$.

Anal. Calcd for $C_9H_{18}ClNO_2$: C, 52.05; H, 8.74; N, 6.74; Cl, 17.07. Found: C, 52.03; H, 9.02; N, 6.51; Cl, 16.97.

1,4-Dioxaspiro[5.5]undecane-9-carbonitrile (27)

Ketone **23** (70.0 g, 0.411 mmol), tosylmethyl isocyanide (TosMIC) (96.4 g, 0.494 mmol) and anhydrous EtOH (28.8 mL, 0.494 mmol) were dissolved in 1,2-dimethoxyethane (1.4 L). *t*-BuOK (60.0 g, 0.535 mmol) was added carefully in small portions at 0 °C with vigorous stirring (CAUTION! Exothermic reaction is observed). The reaction mixture was stirred at 0 °C for an additional 30 min, and then at 50 °C for 30 min and at r.t. overnight. Most of 1,2-dimethoxyethane was evaporated in vacuo, the residue was triturated with *t*-BuOMe (600 mL), and insoluble precipitate was filtered off. The filtrate was evaporated in vacuo, and the product was purified by flash chromatography on silica gel (*t*-BuOMe as eluent).

Yield: 61.8 g (83%); yellowish liquid.

The compound was obtained as ca. 1.2:1 mixture of diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.63 (br s, 4 H), 3.42 (s, 0.55 × 2 H), 3.36 (s, 0.45 × 2 H), 2.91–2.84 (m, 0.45 × 1 H) and 2.44–2.37 (m, 0.55 × 1 H), 2.07 (d, *J* = 13.6 Hz, 1 H), 1.98–1.80 (m, 4 H), 1.78–1.70 (m, 1 H), 1.59–1.50 (m, 1 H), 1.22–1.10 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 129.4, 121.7 and 121.4, 113.9, 74.2, 69.0 and 68.4, 66.4, 59.5 and 59.4, 29.2 and 27.1, 27.3 and 26.5, 23.6 and 22.7.

LC/MS (CI): *m*/*z* = 181 $[M]^+$.

Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.27; H, 8.70; N, 8.10.

1,4-Dioxaspiro[5.5]undecane-9-carboxylic Acid (28)

Nitrile **27** (29.9 g, 0.165 mmol) was heated at reflux in H_2O (190 mL) media in the presence of KOH (37.0 g, 0.660 mmol) for 4 h. The alkaline solution was diluted with toluene (350 mL), the organic phase was separated and discarded. The aqueous phase was acidified with 10 M aq HCl (80 mL) and extracted with EtOAc (3 × 250 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo.

Yield: 23.8 g (72%); yellowish crystals; mp 107–109 °C.

The compound was obtained as ca. 1.2:1 mixture of diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.91 (br s, 1 H), 3.74–3.67 (m, 1 H), 3.67–3.61 (m, 3 H), 3.49 (s, 0.45 × 2 H) and 3.38 (s, 0.55 × 2 H), 2.55–2.43 (m, 0.45 × 1 H) and 2.36–2.22 (m, 0.55 × 1 H), 2.10 (d, *J* = 13.8 Hz, 1 H), 1.96–1.84 (m, 1 H), 1.85–1.73 (m, 3 H), 1.73–1.52 (m, 2 H), 1.20–1.07 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.6 and 181.4, 75.29, 73.0, 70.7, 69.6, 67.0 and 69.9, 60.2 and 59.8, 42.7 and 40.9, 30.1 and 29.9, 23.5 and 22.8.

LC/MS (CI): *m*/*z* = 199 $[M - 1]^-$.

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.08; H, 8.08.

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Supporting Information

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